A Status Report on Chronic Fatigue Syndrome

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Medical history has shown that clinical disease entities or syndromes are composed of many subgroups—each with its own cause and pathogenesis. Although we cannot be sure, we expect the same outcome for chronic fatigue syndrome (CFS), a medically unexplained condition characterized by disabling fatigue accompanied by infectious, rheumatological, and neuropsychiatric symptoms. Although the ailment clearly can occur after severe infection, no convincing data exist to support an infectious (or immunologic) process in disease maintenance. Instead, data point to several possible pathophysiological processes: a covert encephalopathy, impaired physiological capability to respond to physical and mental stressors, and psychological factors related to concerns about effort exacerbating symptoms. Each of these is under intense investigation. In addition, some data do exist to indicate that environmental agents also can elicit a state of chronic fatigue. We expect data to accumulate to support the belief that CFS has multiple causes. ***Key words:*** **brain, cardiovascular, chronic fatigue syndrome, cognition, immunologic, psychiatric, viral.** *Environ Health Perspect* **110(suppl 4):673–677 (2002).**
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Chronic fatigue syndrome (CFS) is one of a group of unexplained illnesses, including fibromyalgia (FM) and irritable bowel syndrome (IBS), whose diagnosis depends on the specialty of the physician to whom the patient turns for help. When evaluated for these unexplained illnesses, the CFS patient often fulfills case definitions for other unexplained illnesses as well (*1*). This overlap has led some investigators to propose that these functional somatic illnesses are variants of one another with little need to identify and label them individually (*2*). However, the clinical similarity of these illnesses does not necessarily mean that they each have the same cause. For example, patients with diffuse pain may sleep poorly and thus develop fatigue, whereas people who have disturbed sleep and inactivity may develop diffuse pain (*3*). If patients with CFS and FM were drawn from the same general population, one would not expect to find differences between these two patient subgroups. That in fact is not the case. We have found that patients with CFS have less functional impairment than those with both CFS and FM (*4*).

Because the diagnosis of FM carries implications as to the clinical status of a CFS patient, we believe it continues to make sense to try to diagnose each of these medically unexplained illnesses. Because there is no objective biomedical marker for CFS, the diagnosis is based on clinical case definitions. The case definitions for the diagnosis of CFS (*5,6*) grew out of the fact that severe fatigue and flu-like symptoms—often beginning suddenly—were thought to reflect underlying viral infection. Thus, the diagnostic criteria for CFS are fulfilled when a patient has at least 6 months of new-onset, medically unexplained fatigue accompanied by at least four of eight identified infectious, rheumatological, and neuropsychiatric symptoms. The illness is common, appearing in more than 0.4% of the population (*7*), with a male-to-female ratio of approximately 1 to 4, and is often disabling; patients with CFS report debility worse than a similar demographic sample of patients with congestive heart failure (*8*).

Infectious and Immunologic Factors

The early idea that CFS represented a form of chronic Epstein-Barr infection was quickly dropped when data were reported indicating that elevated Epstein-Barr virus titers, reflecting prior infection, are not uncommon in healthy people (*9*). Reports on the possibility of the illness being caused by chronic infection by other agents, including enteroviruses (*10*), human herpesvirus 6 (*11*), *Mycoplasma* (*12*), retroviruses (*13*), Borna disease virus (*14*), parvovirus B19 (*15*), and "stealth" viruses (*16*), continue to appear, but confirmation and replication are lacking (*17–20*). Infection can certainly trigger the onset of CFS, and patients reporting a sudden, viral-like onset to their illness report this occurring in winter months (*21*). Elevated rates of a CFS-like illness are known to follow infectious mononucleosis (*22*), Lyme disease (*23*), and severe viral infection (*24*). Thus, post-infectious fatigue exists, but persistence of an infectious agent has not been demonstrated. Obviously covert infections such as chronic sinusitis warrant careful consideration and, if diagnosed, require adequate treatment. Patients do complain of sensitivity to frequent upper respiratory infections, but it is not clear if these really do reflect infection or instead represent allergic or nonallergic rhinitis. These two symptom-producing conditions are very common in CFS—occurring, respectively, in 30% and 46% of CFS patients (*25*).

If persistent infection is not the cause, another hypothesis is that CFS is infection-triggered immunologic activation or dysregulation. A number of papers have reported immune activation in CFS [for review, see (*26,27*)]. The critical research issue is to determine if these changes are the consequence of an underlying etiological mechanism producing the symptoms of CFS or, instead, occur because of secondary psychophysiological changes wrought by the disease, such as inactivity, disturbed sleep, and/or chronic stress. When we matched our CFS group with controls who, like the patients, were sedentary, we could find no evidence of immunologic dysfunction in the patient group (*28*). Interestingly, some differences did emerge in a group of Gulf War veterans (GVs) who developed CFS in a quasi-epidemic pattern; we think we were able to find these differences because the veterans as a group were immunologically more homogeneous than the civilians as a group.

Despite our inability to find specific cytokine or cell-surface-marker abnormalities in nonveteran CFS patients, other data do support some underlying immunologic problem: *a*) some CFS patients appear to have an antibody against a specific nuclear antigen (*29*), *b*) patients have a dysregulated 2,5-A/RNase L antiviral defense pathway (*30,31*), and *c*) treatment with an immune-active agent, mismatched RNA, may reduce disability (*32*) (a study to replicate this outcome is currently under way).

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Psychiatric Factors

A very different set of hypotheses considers CFS a variant of major depressive disorder or simply a manifestation of somatization disorder (SD). Regarding major depressive disorder, CFS patients—even those with concurrent major depression—are phenomenologically different from patients with major depression alone. CFS patients have less self-reproach and more somatic symptoms than depressed patients (*33*) [i.e., the cognitive styles of CFS and major depression differ (*34*)], less disturbed personalities (*35*), and a different immunologic profile (*36*). Determining whether CFS is a manifestation of SD is a harder question. There is no doubt that CFS is the modern equivalent of neurasthenia (*37*). But that observation leaves the question: What is neurasthenia?

The diagnosis of SD depends on the beliefs of the medical evaluator and the diagnostic assessment tool used. If the evaluator applies the subsyndromal diagnostic criteria of Escobar et al. (*38*) and reflects the belief that CFS symptoms are of a psychiatric nature, then nearly every CFS patient will be shown to have SD. However, if the CFS symptoms are coded as physical and strict *Diagnostic Manual of Mental and Behavioral Disorders-III-R* criteria are applied, only 2.3% of patients have SD (*39*).

Just because it is not clear how to diagnose SD in CFS patients does not mean that CFS patients do not have this disorder. An Australian group (*40*) using factor analysis of symptom self-report data found that 22% of CFS patients reported a large number of somatic symptoms. This group of patients had a high probability of having concurrent psychiatric disorder. They were labeled "somatizers." The remaining patients in this study had fewer somatic symptoms and less psychopathology. Similar results led American researchers to suggest that the case definition for CFS be changed so that the diagnosis would be given only to those patients with relatively few symptoms (*41*). This strategy would exclude patients with possible SD.

Another approach might be to exclude patients with a positive history for major psychopathology beginning before CFS onset and then to stratify on the basis of the existence of a current major psychiatric disorder; this tactic would use the existence of psychopathology as a marker of SD. To test if this idea would work, we rank-ordered our patients on the basis of their illness severity ranging from category 1 to category 6 (*42*): category 1 included patients fulfilling the more rigorous 1988 case definition (*5*) as well as reporting symptom intensities of ≥ 3 on 0–5 severity scales; categories 2–5 were progressively less severe rankings. Category 6 included patients who fulfilled the 1994 but not the 1998 case definition and had symptom severities < 3. CFS severity in those with Axis I co-morbidity (n = 19) tended to be higher (median [M] = 1) than in those without comorbidity (n = 48; M = 2; $p < 0.14$). However, the difference in symptom severity between the groups was small. This result means that practitioners cannot assume SD in patients with psychiatric comorbidity. However, they should look for this comorbidity and treat it when it exists.

In contrast to efforts to predict or identify somatization, we have arrived at a concrete marker of increased risk for major psychopathology (*4*). This occurs when patients have multiple medically unexplained syndromes. In evaluating our patients, each receives a standardized psychiatric diagnostic interview as well as assessments for FM or for IBS. The prevalence of lifetime major depression was 36% of 31 patients with CFS alone, 57% of 28 patients with both CFS and FM, and 73% of 22 patients with CFS, FM, and IBS ($\chi^2 = 7.45$; $p < 0.05$). We interpret these results to mean that patients bearing three concurrent medically unexplained syndromes (multiple chemical sensitivity can be substituted for IBS) may be considered to have psychopathology and should routinely be sent for psychological or psychiatric evaluation and possible treatment. It will be very important for future research studies to provide information on the constitution of their subjects. Obviously, if study samples are skewed toward groups having multiple concurrent medically unexplained syndromes, this could result in outcomes that support psychiatric factors in the genesis of CFS, whereas studies of patients with CFS alone might be more useful in efforts to identify biomedical markers of the illness.

Behavioral Factors

The U.K. group in London that studies CFS has focused on disease maintenance, and their 1998 book *Chronic Fatigue and Its Syndromes* is good reading for those seeking detailed information on CFS (*43*). Wessely et al. believe that person factors interact with illness triggers and subsequent deconditioning to prolong illness duration. Thus, people with a tendency for mood problems or amplification of somatic sensations might become worried about activity-related symptoms after some viral illness and thus reduce activity further. They support this line of thinking with their successful trials (*44,45*) of cognitive behavioral therapy (CBT).

Although this model may explain continued illness in some CFS patients, it certainly does not pertain to all CFS patients and is thus not too satisfactory. In contrast to the above scenario is the previously well patient who presents to her doctor for the first time with an apparent flu of sudden onset that never goes away and who continues her former life—albeit at reduced levels of activity. When evaluated, such patients frequently do not have the sort of negative person factors and activity-related fears identified in the U.K. researchers' model.

The CBT story is also not clear-cut. The success of CBT as a treatment points to a role for person factors in the perception of symptom severity, but one cannot make further inferences about such factors in the genesis of illness. This is because CBT is useful in treating any chronic illness—medical as well as psychiatric. For example, CBT reduces symptom severity in patients with known medical disease such as rheumatoid arthritis (*46*). Inferring that CFS is a psychogenic disorder because of the success of CBT is risky for a second reason, as well: Not all CBT trials are effective in relieving the symptoms of CFS (*47*). Friedberg and Krupp suggest that CBT did not help their patients because they were not too disabled by their illness. Indeed, in trying to understand CFS, it would make sense to focus on the higher functioning patients—those who have fewer problems with secondary factors produced by the illness such as poor sleep, inactivity, and chronic stress.

Orthostatic Intolerance

Another hypothesis for illness maintenance has to do with cardiovascular abnormalities and the patient complaint of feeling much worse while standing. A report from Johns Hopkins indicated that a majority of CFS patients developed delayed orthostatic hypotension and that symptoms disappeared after treatment using either volume expansion or beta blockers (*48*). However, we found no difference in orthostatic intolerance between unmedicated CFS patients (i.e., not even taking low doses of tricyclic antidepressants) and sedentary healthy controls (*49*). Using a noninvasive technique called impedance cardiography, we did, however, find the CFS group to have lower stroke volumes, even in baseline conditions. Whether this finding indicates a covert cardiac problem or one secondary to reduced blood volume remains a research question; both of these have been suggested (*50,51*). We have repeated our studies of cardiac stroke volume and have found it to be lowest in patients with the most severe symptoms (*52*). This result does suggest that low cardiac output could be playing a role in the genesis of postexertional fatigue, a common complaint in CFS patients. We are currently extending these studies to tests of cardiac function using standard clinical radioisotope techniques (i.e., multiple gated acquisition scans).

Our data indicate that tilt testing is not a sensitive way to diagnose orthostatic intolerance in CFS, with two provisos. First, it is

reasonable for the physician to monitor heart rate and blood pressure after 5 min of supine rest and then every minute for 5 min of standing. Some patients may show a dramatic postural tachycardia (*53*) or other orthostatic change (*54*) within this brief time frame. When present, these should be treated. Second, tilt may be a better diagnostic tool for children than for adults. A recent controlled study showed adolescents with CFS to be highly sensitive to orthostatic challenge (*55*).

Finally, data do exist to suggest that a risk factor for developing CFS may be impaired work capacity. Individuals who develop chronic fatigue after infectious mononucleosis tend to be those with lower physical fitness (*56*). A number of studies have evaluated fitness by using exercise treadmill testing. One early study suggested that CFS patients were less fit (perhaps deconditioned) relative to healthy controls (*57*). Although this study was flawed in its not using sedentary healthy people as controls, two other studies controlled for the inactivity in patients and still found the same result (*58,59*). Data from another study suggested that subtle reductions in blood volume might have been responsible for the reduced peak oxygen consumption found (*60*). Inbar et al. (*59*) found an unexpectedly slow increase in heart rate and lower peak heart rate values in controls, leading them to conclude that these findings were not consistent with deconditioning in CFS. In contrast to reports suggesting impaired work capacity in CFS, a number of other groups (*61,62*), including our own (*63*), have not been able to confirm differences in work capacity between CFS patients and controls. Of great interest are data from the Seattle CFS twin study (*64*). They also showed no significant difference in indices of fitness or work capacity between healthy twins and twins with CFS. However, the study found both sets of twins to have extremely low VO_2 maximum values after exercise (*64*). This suggests that impaired metabolic capacity to respond to exercise may be a risk factor for developing CFS.

Inbar et al. (*59*) noted a hypodynamic cardiac response in terms of heart rate exercise. They concluded that this may be "a disease-specific physiological attribute, leading to low cardiac output and early onset of fatigue" with reduced exercise capacity. We have found a similar hypodynamic response of the endocrine system to exercise challenge (*65*) and of the cardiovascular system to a stressful cognitive probe (*66*). In fact, we found that those patients who showed the lowest blood pressure response to the stressor reported the most severe symptoms. These data support a role for these physiological systems in producing the common patient complaint of symptoms worsening after both physical and mental stressors.

Covert Encephalopathy

One of the most common complaints of CFS patients are difficulties paying attention to and memorizing new information. Although some groups have shown that objective cognitive difficulties exist, particularly in the encoding of information, others have not found evidence of cognitive dysfunction in patients with CFS [for review, see Tiersky et al. (*67*)]. The major focus of our own work evaluates the possibility that some CFS patients have a mild encephalopathy associated with their illness. Initially, we found that CFS patients had significant cognitive abnormalities (*68*). We repeated our studies after stratifying patients based on the presence or absence of major psychiatric diagnosis beginning after CFS onset. The group with no psychiatric diagnoses was the one with the most cognitive dysfunction (*69*). Next, we showed that these cognitive abnormalities correlated with functional status in that the more cognitive the impairment, the more the patient reported cutting down on her normal activities (*70*). Then we did a study in which two neuroradiologists, blinded to group, evaluated the brain magnetic resonance images (MRIs) of CFS patients and controls (*71*). Our a priori hypothesis that CFS patients with no major psychiatric disorders would have the most abnormalities was confirmed: 66% of that group had abnormalities in contrast to 30% of the group with major psychiatric diagnoses and 22% of the control group. The abnormalities found were subtle, most commonly small T_2-weighted lesions (version of MRI that shows lesions containing water) in frontal lobes. Finally, we asked whether the presence of an abnormality had any consequences on functional status. If these lesions were simply epiphenomena of the illness, we would expect no relation. But if the lesions were involved in the pathogenetic process, a relation might emerge. We found that the group with abnormalities reported significantly poorer physical functioning on the Short Form-36 (SF-36), a common disability assessment tool (*72*). Although in this study we found the presence of small lesions in the group of CFS patients who also showed the most cognitive impairment in related studies (*69*), the low number of lesions present made it difficult to explain the cognitive dysfunction measured. Therefore, we next quantitatively assessed cerebral ventricular volumes in CFS patients to get a more subtle indication of brain involvement. The results of a pilot study suggested that ventricular volumes in CFS patients may be larger than those in healthy controls (*73*), a finding that currently awaits further confirmation.

In a set of studies trying to link cognitive function with underlying brain function, we conducted a set of functional magnetic resonance imaging studies and found that CFS patients had more diffuse activation in the posterior regions of the brain than did healthy controls. Based on other studies, this pattern of activation indicates that cognitive work may be more effortful for CFS patients—a finding that one might expect with subtle brain disease. Our interpretation of all these data is that some CFS patients may have a subtle brain problem.

Environmental Causes

Behan (*74*) has noted that some patients with well-documented chronic exposure to organophosphates develop a syndrome that sounds very much like CFS, and cases of CFS have been reported to follow ciguatera poisoning and exposure to solvents (*75*). Supporting the idea that environmental contaminants are associated with CFS is an unreplicated report of increased organochlorine levels in patients with CFS (*76*).

The biggest drive to the hypothesis that toxic chemicals could cause CFS is an outgrowth of the Gulf War. Nearly 10% of deployed American troops returned home with a host of medically unexplained symptoms—primarily fatigue, musculoskeletal achiness, and cognitive dysfunction. In a survey of healthcare-seeking GVs, we found that 16.1% reported symptoms consistent with CFS (*77*) and that, on careful clinical evaluation, many fulfilled the published case definition for CFS (*42*); finding CFS as a common diagnosis in symptomatic GVs has been reported by others, as well (*78*). The problem with linking toxic factors with CFS is that veterans did not suffer symptoms of acute exposure to such factors. Despite this lack of symptoms, veterans did have exposures. Nearly all GVs used insecticides, some took pyridostigmine bromide as an antidote to possible nerve gas exposure, and some were probably exposed to subclinical doses of Sarin, one of the most toxic nerve gases that exists. Although the common belief was that individuals had to have had acute symptoms of intoxication in order to evince chronic symptoms, more recent evidence does suggest that symptoms can develop in individuals who do not report definite episodes of acute toxicity (*79,80*).

Although one group did publish data suggesting that there were discrete Gulf War syndromes (*81*)—some of which correlated with different exposures (*82*), no other group has been able to replicate this result. To the contrary, available data indicate that there is no unique constellation of symptoms related to participation in the Persian Gulf conflict (*83,84*). Of great interest, however, is the

Table 1. Demographics of CFS center patients.

	No major psychiatric diagnosis	Major psychiatric diagnosis after onset
Total	135	68
No. working	61 (45.2%)	33 (48.5%)
No. Caucasian	127 (94.1%)	62 (91.2%)
Age (years)		
18–20	2 (1.5%)	1 (1.5%)
20–29	30 (22.2%)	14 (20.6%)
30–39	47 (34.8%)	27 (39.7%)
40–49	43 (31.9%)	20 (29.4%)
≥50	13 (9.6%)	6 (8.8%)

report that symptomatic GVs had a higher probability of receiving multiple vaccinations while at the Persian Gulf than did healthy GVs (*85*).

The symptom complex found in GVs occurs in veterans deployed to theaters outside the Persian Gulf (*86*) as well as in nondeployed veterans (*84*). The fact that CFS is thought to occur relatively frequently in overseas development workers (*87*) does raise the possibility of another common variable occurring during deployment and conflict—stress. Supporting a role of possible stress in the genesis of the GVs' medically unexplained fatigue is a 50% rate of post-traumatic stress disorder (PTSD) in 76 GVs with CFS or its less severe counterpart, idiopathic chronic fatigue (ICF) (*88*); in contrast, PTSD occurs in only about 1% of nonveteran CFS patients. However, stress is no less benign than toxic exposures; veterans with PTSD are known to suffer significant hippocampal neuronal loss (*89*).

Although epidemiologic evidence does not support the idea of a unique Gulf War syndrome, data do exist to support the inference that service in the Persian Gulf has pathological consequences: *a*) GVs with CFS/ICF have objectively measured cognitive impairment (*90*); *b*) one study reported that GVs have abnormal peripheral nerve function compared with civilian controls (*91*), and our own work noted elevated thresholds to fine touch but not to heat in GVs with CFS/ICF compared with healthy GVs—of great interest was the finding that the healthy GV group had elevated thresholds relative to those of a civilian control group (*92*); and *c*) a number of abnormalities of central nervous system origin have been found in symptomatic GVs (*93*).

Assuming that large numbers of GVs experienced both stress and/or potential toxic exposures, the question that immediately comes up is why only 10% of the entire group developed symptoms. One group has done some genetic testing and has found significant decreases in one specific arylesterase in sick GVs compared with healthy GVs. This enzyme system is involved in destroying via hydrolysis organophosphate anticholinesterase poisons (*94*). Because the decrease in this enzyme was only one of several statistical comparisons made, the possibility of a type 1 statistical error existing (i.e., the finding occurred simply by chance) is a real one. However, we have analyzed plasma samples and have been able to replicate this finding: symptomatic GVs with abnormal neuropsychological test results have significantly lower levels of this enzyme than either symptomatic GVs with normal neuropsychological test results or healthy GVs (*95*).

CFS Research in the Twenty-First Century

To summarize, CFS is a clinical disease entity with no lab test to corroborate diagnosis. Thus, like other syndromes, it probably is heterogeneous, with several different pathogenetic paths leading to the same end result—the patient with severe fatigue and other constitutional symptoms. Initial focus on discrete viral and immunologic causes continues but is on the wane. Table 1 shows the demographic composition of the 203 CFS patients who had no major psychopathology in the 5 years before the onset of their CFS whom we have studied in our center over the past 8 years. Without a doubt, some have SD, but how does a physician identify those patients? In contrast, some patients have low cardiac stroke volumes and others have the suggestion of a mild encephalopathy. Our plan is to determine if subsets of CFS patients have identifiable medical causes that will ultimately be treatable.

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